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REVIEW ARTICLE

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Contemporary Lipid-Lowering Strategies in Patients with Subclinical Coronary Atherosclerosis and Moderate Coronary Artery Calcification (CACS 100-299 AU)

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Abstract

Subclinical coronary atherosclerosis represents one of the earliest detectable manifestations of coronary artery disease and is associated with an increased risk of future cardiovascular events. Coronary artery calcium scoring (CACS) is a well-established non-invasive imaging biomarker that complements conventional cardiovascular risk prediction models and improves risk stratification, particularly in asymptomatic individuals with borderline or intermediate estimated cardiovascular risk. Accumulating evidence indicates that a moderate coronary artery calcium score (CACS 100–299 AU) is associated with a substantially increased risk of future cardiovascular events compared with that estimated by traditional risk prediction models alone. Consequently, CACS may facilitate the timely initiation and appropriate intensification of lipid-lowering therapy. This review summarizes the current evidence regarding the management of dyslipidemia in patients with subclinical coronary atherosclerosis and a moderate coronary artery calcium score (CACS 100–299 AU), with particular emphasis on contemporary therapeutic strategies and recent advances in lipid-lowering treatment. (**International Journal of Biomedicine. 2026;16(4):419-429**.)

Keywords: coronary artery calcium • coronary artery calcium score • dyslipidemia • subclinical coronary atherosclerosis • lipid-lowering therapy • cardiovascular risk stratification • primary prevention

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Introduction

Subclinical atherosclerosis is defined as the presence of structural atherosclerotic changes within one or more vascular territories before the onset of clinically manifest cardiovascular disease. It represents one of the earliest detectable manifestations of atherosclerotic disease, and its identification has become increasingly important in contemporary preventive cardiology, as it enables cardiovascular risk assessment before clinical events.[1]

Cardiovascular disease (CVD) remains the leading cause of mortality both in Europe and worldwide despite substantial advances in prevention and treatment. Current epidemiological projections indicate that the global burden of CVD will continue to increase over the coming decades, with ischemic heart disease remaining the most prevalent cardiovascular disorder.[2]

Coronary artery disease (CAD) remains one of the leading causes of death and disability worldwide, accounting for approximately seven million deaths annually. Although the incidence of CAD has declined in many high-income countries owing to improvements in preventive strategies and evidence-based therapies, its overall burden continues to increase due to population aging and the rising prevalence of cardiometabolic risk factors.[3] The classical cardiovascular risk factors identified in the Framingham Heart Study established the foundation of contemporary preventive cardiology and introduced the concept of cardiovascular risk prediction.[4] Subsequently, the

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INTERHEART study demonstrated that the vast majority of myocardial infarctions worldwide are attributable to a limited number of potentially modifiable cardiovascular risk factors.[5] Furthermore, validation of the SCORE2 algorithms in the EPIC-Norfolk cohort demonstrated satisfactory predictive performance in middle-aged individuals while highlighting important limitations in risk discrimination among older adults.[6]

Data from the CARDIA study, which included 3,980 participants aged 22–36 years, demonstrated that the Framingham Risk Score (FRS) frequently underestimates cardiovascular risk in young adults because chronological age is a dominant component of the algorithm. Consequently, individuals with prolonged exposure to multiple cardiovascular risk factors may remain classified as low risk despite already having developed subclinical atherosclerosis.[7]

Similar findings were reported in a cohort of 2,447 asymptomatic women, in whom a substantial proportion of individuals with coronary artery calcification were still classified as being at low cardiovascular risk according to conventional risk assessment tools.[8] Collectively, these observations indicate that conventional cardiovascular risk prediction models may underestimate the true burden of subclinical coronary atherosclerosis in a considerable proportion of asymptomatic individuals.

Endothelial dysfunction is a key pathophysiological mechanism across the entire spectrum of atherogenesis and independently predicts future cardiovascular events, regardless of conventional cardiovascular risk scores.[9] Accordingly, assessment of endothelial function has emerged as an additional tool for cardiovascular risk stratification. A meta-analysis including 32 studies and more than 15,000 participants demonstrated that impaired endothelial function, assessed by peripheral arterial tonometry or brachial artery flow-mediated dilation during reactive hyperemia, is independently associated with an increased risk of future cardiovascular events.[10]

Taken together, these findings support the use of non-invasive imaging modalities, particularly coronary artery calcium scoring (CACS) and coronary computed tomography angiography (CCTA), for the detection of subclinical coronary atherosclerosis and refinement of cardiovascular risk stratification. Particular attention should be paid to asymptomatic individuals with a moderate coronary artery calcium score (CACS 100–299 AU), in whom cardiovascular risk is frequently underestimated by conventional risk prediction models such as SCORE2 and SCORE2-OP. Early initiation and appropriate intensification of lipid-lowering therapy in these patients may reduce cumulative exposure to LDL cholesterol and slow the progression of atherosclerotic plaque development.[11]

The rapid development of novel lipid-lowering therapies has substantially expanded the therapeutic armamentarium for the management of dyslipidemia. In addition to statins and ezetimibe, PCSK9-targeted therapies, bempedoic acid, inclisiran, and emerging RNA-based therapeutic approaches are progressively reshaping contemporary lipid management, while several additional therapeutic strategies remain under active clinical investigation.

Materials and Methods

This narrative review was based on a literature search performed in the PubMed/MEDLINE database covering publications from January 2000 to January 2025. The search strategy included the following keywords and MeSH terms: “coronary artery calcium score,” “subclinical atherosclerosis,” “coronary artery calcification,” “dyslipidemia,” and “lipid-lowering therapy”. Original research articles, systematic reviews, meta-analyses, narrative reviews, and relevant clinical practice guidelines published in English were considered for inclusion. Publications were selected based on their relevance to coronary artery calcium assessment, cardiovascular risk stratification, and the role of lipid-lowering therapies in patients with subclinical coronary atherosclerosis.

Publications were excluded if they were duplicate records, editorials, letters to the editor, or not directly relevant to the objectives of this review. Preference was given to peer-reviewed full-text publications; however, conference proceedings were included when they provided relevant information that complemented the available published evidence.

Additional relevant studies were identified by manually screening the reference lists of selected publications and major guideline documents from the European Society of Cardiology (ESC), European Atherosclerosis Society (EAS), and American College of Cardiology/American Heart Association (ACC/AHA). The available evidence was synthesized narratively according to the main themes of this review.

Pathogenesis and Clinical Significance of Atherosclerosis

Atherosclerosis is a chronic inflammatory disease that underlies the development of both cardiovascular and cerebrovascular disorders and is characterized by lipid accumulation and plaque formation within the arterial intima.[12,13] Endothelial dysfunction represents the initiating event in atherogenesis by facilitating the retention of low-density lipoprotein (LDL) particles within the arterial wall and triggering a local inflammatory response. Subsequently, circulating monocytes infiltrate the vessel wall, differentiate into macrophages, and internalize oxidized LDL (oxLDL), leading to the formation of lipid-laden foam cells. Migration and proliferation of vascular smooth muscle cells promote the development of a fibrous cap, whereas plaque rupture or erosion activates platelets and the coagulation cascade, ultimately resulting in thrombus formation.[14,15]

Assessment of plaque stability has become a cornerstone of contemporary cardiovascular risk evaluation.[13] The randomized SCOT-HEART trial demonstrated that patient prognosis is determined not only by the severity of coronary stenosis but also by plaque characteristics. In particular, the presence of high-risk plaque features was independently associated with an increased incidence of future cardiovascular events.[16]

Lipid-lowering therapy has consistently been shown to reduce cardiovascular morbidity and mortality.[17] Furthermore, evidence from multiple cohort studies and meta-analyses

indicates that early initiation of lipid-lowering therapy is justified in individuals with elevated LDL cholesterol concentrations (>130 mg/dL), particularly when additional cardiovascular risk factors are present.[18,19]

Imaging Modalities for the Assessment of Subclinical Atherosclerosis

The 2021 European Society of Cardiology (ESC) Guidelines introduced the SCORE2 and SCORE2-Older Persons (SCORE2-OP) algorithms for estimating the 10-year risk of fatal and non-fatal cardiovascular events in apparently healthy individuals.[20,21] According to these models, cardiovascular risk categories are defined according to age as follows: low-to-moderate risk (<2.5% for individuals <50 years, <5% for those aged 50–69 years, and <7.5% for those ≥70 years), high risk (2.5–7.5%, 5–10%, and 7.5–15%, respectively), and very high risk (≥7.5%, ≥10%, and ≥15%, respectively).[22]

Despite the availability of several cardiovascular risk prediction models, none directly assesses the extent of arterial wall remodeling or the burden of subclinical atherosclerosis.[23] Consequently, additional imaging techniques have been incorporated into cardiovascular risk assessment to enable a more individualized evaluation. These include carotid intima-media thickness (CIMT), pulse wave velocity (PWV), coronary artery calcium scoring (CACS), and coronary computed tomography angiography (CCTA).

In a population-based cross-sectional study involving 3,087 individuals without established cardiovascular disease or diabetes mellitus, pulse wave velocity (PWV >10 m/s) and coronary artery calcium burden, assessed by computed tomography, were evaluated. Individuals classified as being at high cardiovascular risk exhibited significantly greater coronary calcification, supporting the value of CACS for identifying subclinical vascular disease.[24] Carotid intima-media thickness (CIMT), measured by ultrasonography, represents another important imaging marker of subclinical atherosclerosis. Numerous studies have demonstrated that CIMT independently predicts future cardiovascular events beyond traditional cardiovascular risk factors.[25] Moreover, longitudinal progression of CIMT correlates with the subsequent risk of cardiovascular disease.[26]

Coronary artery calcification constitutes an integral component of the atherosclerotic process, and the coronary artery calcium score reflects the overall atherosclerotic burden within the coronary circulation.[27,28] Coronary artery calcium is currently regarded as the most extensively validated non-invasive imaging biomarker of subclinical coronary atherosclerosis. The presence of coronary calcification strongly correlates with underlying coronary atherosclerosis, whereas its absence substantially reduces—although does not completely exclude—the likelihood of significant obstructive coronary artery disease.[29]

According to the Agatston classification, coronary artery calcium burden is categorized as follows: CACS = 0, no detectable coronary calcification; CACS 1–99 AU, mild coronary calcification; CACS 100–299 AU, moderate coronary calcification; and CACS ≥300 AU, severe coronary calcification associated with a markedly increased cardiovascular risk.[29,30]

Current evidence supports intensification of preventive therapy according to the degree of coronary calcification. Individuals with CACS 1–99 AU generally benefit from moderate-intensity statin therapy, whereas those with a moderate CACS (100–299 AU) should be considered for moderate- to high-intensity statin therapy following an individualized assessment of overall cardiovascular and bleeding risk. Patients with CACS ≥300 AU are usually managed with intensive lipid-lowering therapy because their cardiovascular risk approaches that observed in secondary prevention populations.[30]

The Multi-Ethnic Study of Atherosclerosis (MESA), including 1,391 low-risk individuals, demonstrated that a CACS >100 AU was associated with a substantially increased incidence of cardiovascular events, highlighting its value for cardiovascular risk reclassification.[31] Likewise, in a prospective study of 117 postmenopausal women, CACS values were significantly higher among those with subclinical coronary atherosclerosis, with a considerable proportion exhibiting CACS >100 AU or >400 AU.[32]

Coronary artery calcium scoring has particular clinical value because conventional risk prediction models, including the Framingham Risk Score and SCORE2/SCORE2-OP, do not consistently identify all individuals at increased cardiovascular risk. Furthermore, CACS may modify the diagnostic strategy in patients with a low pre-test probability of obstructive coronary artery disease.[33] Incorporation of CACS into SCORE2/SCORE2-OP has been shown to improve cardiovascular risk classification, reclassifying approximately 48% of individuals initially categorized as high risk into a lower-risk category, while identifying approximately 7% of individuals initially considered low or intermediate risk as being at high cardiovascular risk.[34] Similarly, a study including 1,461 asymptomatic individuals with at least one cardiovascular risk factor demonstrated that combining the Framingham Risk Score with CACS provided superior cardiovascular risk discrimination compared with either method alone.[35]

In adults younger than 45 years, CACS may provide incremental value for cardiovascular risk stratification, particularly in individuals with a family history of premature cardiovascular disease, multiple cardiovascular risk factors, or borderline estimated risk, because conventional 10-year risk prediction models may substantially underestimate lifetime cardiovascular risk.[29]

From a clinical perspective, individuals with a moderate coronary artery calcium score (CACS 100–299 AU) represent an important subgroup in whom therapeutic decision-making remains challenging. Increasing evidence suggests that the actual cardiovascular risk in many of these patients is considerably higher than that estimated by conventional risk prediction models. Consequently, this population may benefit from earlier initiation and more intensive lipid-lowering therapy than would otherwise be recommended based solely on traditional risk calculators.

In conclusion, moderate coronary artery calcium (CACS 100–299 AU) provides incremental prognostic information beyond conventional cardiovascular risk prediction models and represents an important imaging biomarker for identifying asymptomatic individuals who may benefit from earlier and more intensive lipid-lowering therapy.

Lipid-Lowering Therapy

The management of dyslipidemia in patients without established cardiovascular disease is multifaceted and includes lifestyle modification, adherence to a heart-healthy diet, regular physical activity, weight control, and smoking cessation.[36] Contemporary pharmacological treatment includes 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), cholesterol absorption inhibitors (ezetimibe), bile acid sequestrants, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, microsomal triglyceride transfer protein (MTP) inhibitors, mipomersen, fibrates, omega-3 fatty acids, and cholesteryl ester transfer protein (CETP) inhibitors,[37] as well as emerging targeted therapies and nanoparticle-based drug delivery systems.

Statins

Statins are the first-line pharmacological agents for the treatment of hypercholesterolemia. They reversibly inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase, thereby reducing serum concentrations of total cholesterol, LDL cholesterol (LDL-C), and, to a lesser extent, triglycerides.[38] A substantial reduction in serum cholesterol levels is usually observed after 4–6 weeks of treatment.[39] Different statins exhibit broadly comparable pleiotropic effects and overall safety profiles.[40] Statin therapy is recommended for primary prevention in patients at moderate, high, or very high cardiovascular risk, as well as for secondary prevention in patients with established cardiovascular disease.[41]

Prospective and observational studies have shown that atorvastatin, simvastatin, and rosuvastatin may reduce LDL-C levels by up to 49% after 12 weeks of treatment and may slow the progression of non-calcified and low-attenuation atherosclerotic plaques. In patients with established atherosclerotic cardiovascular disease, statin therapy has been associated with an increase in calcified plaque volume and a reduction in non-calcified plaque burden, suggesting plaque stabilization and favorable remodeling of atherosclerotic lesions.[42–45] Statin therapy reduces relative cardiovascular risk by approximately 20–30%, largely irrespective of baseline LDL-C levels.[46] Meta-analyses and systematic reviews have demonstrated that statins reduce the risk of myocardial infarction, stroke, major adverse cardiovascular events, and all-cause mortality without a significant increase in myalgia, elevated hepatic transaminases, or diabetes mellitus. In primary prevention among patients with moderate to high cardiovascular risk, statins reduce coronary events by up to 30%, myocardial infarction by up to 31.7%, and cerebrovascular events by up to 14.4%, although a consistent significant reduction in all-cause mortality has not been uniformly demonstrated.[47–49]

The intensity of lipid-lowering therapy in patients at moderate cardiovascular risk should be individualized according to the overall cardiovascular risk profile. High-intensity statin therapy, defined as atorvastatin 40–80 mg or rosuvastatin 20–40 mg, is expected to reduce LDL-C levels by >50%, whereas moderate-intensity statin therapy, such as atorvastatin 10–20 mg or rosuvastatin 5–10 mg, typically achieves an LDL-C reduction of 30–50%.[37] Meta-analyses of large randomized trials have shown that each 1 mmol/L reduction in LDL-C is associated with an approximately 20% reduction in the risk of major vascular events, with an acceptable safety profile for more intensive statin therapy.[50] In patients with acute coronary syndromes, high-intensity statin therapy significantly reduces mortality and recurrent cardiovascular events, whereas the magnitude of benefit appears less pronounced in patients with stable coronary disease.[51–53] The greatest absolute reduction in cardiovascular morbidity and mortality is observed in patients at higher baseline risk, supporting a more intensive lipid-lowering strategy in this population.[54]

Ezetimibe

Ezetimibe, an inhibitor of intestinal cholesterol absorption, lowers LDL-C concentrations by approximately 15–20% when administered either as monotherapy or in combination with statins. The combination of high-intensity statin therapy and ezetimibe is more effective in reducing LDL-C levels than statin monotherapy.[55,56] An observational study including 17,830 patients showed that the addition of ezetimibe was associated with an additional LDL-C reduction of up to 14.8% and tripled the likelihood of achieving guideline-recommended LDL-C targets.[57] This may be particularly relevant in patients with subclinical coronary atherosclerosis and a moderate coronary artery calcium score (CACS 100–299 AU), in whom more intensive LDL-C reduction may help slow the progression of atherosclerotic plaque burden.

PCSK9 Inhibitors

By inhibiting proprotein convertase subtilisin/kexin type 9 (PCSK9), monoclonal antibodies against PCSK9 reduce serum concentrations of total cholesterol, LDL-C, apolipoprotein B, and lipoprotein(a) [Lp(a)].[5] They are indicated in patients who fail to achieve guideline-recommended LDL-C targets despite maximally tolerated conventional lipid-lowering therapy.[59,60] Evolocumab and alirocumab provide additional LDL-C reduction when administered in combination with moderate- or high-intensity statin therapy, as confirmed by a network meta-analysis of randomized clinical trials.[61] These fully human monoclonal antibodies are used in patients with primary hypercholesterolemia who do not achieve LDL-C targets or who are intolerant to statins.[62,63] Oral PCSK9 inhibitors are currently under clinical development and may further expand therapeutic options in the future.[64]

Fibrates

Fibrates exert their lipid-modifying effects through activation of the nuclear peroxisome proliferator-activated receptor alpha (PPAR-α).[65] They reduce endogenous production of very-low-density lipoproteins (VLDL) and enhance their clearance. In addition, fibrates increase serum high-density

lipoprotein cholesterol (HDL-C) concentrations, whereas their effect on LDL-C is comparatively modest.[66] They are primarily indicated in patients with hypertriglyceridemia and mixed dyslipidemia.[67] Combination therapy with a statin and a fibrate produces greater improvement in the lipid profile than statin monotherapy in patients with mixed hyperlipidemia,[68] a finding further supported by meta-analysis.[69] Pemafibrate, a newer selective PPAR-α modulator, has been shown to significantly reduce triglycerides, VLDL cholesterol, and total cholesterol while increasing HDL-C concentrations.[70]

Mipomersen

Mipomersen is an antisense oligonucleotide targeting human apolipoprotein B-100 (apoB-100). By binding directly to hepatic apoB messenger RNA, it inhibits apoB-100 synthesis and thereby reduces plasma concentrations of total cholesterol, LDL-C, and apoB. The drug has been used in patients with homozygous familial hypercholesterolemia or refractory heterozygous familial hypercholesterolemia.[71] A randomized double-blind trial demonstrated that adding mipomersen to maximally tolerated lipid-lowering therapy reduced LDL-C levels by up to 36.9%, together with reductions in apolipoprotein B and Lp(a), markers closely related to atherogenic lipoprotein burden. These effects may contribute to slowing atherosclerosis progression in patients with familial hypercholesterolemia.[72]

Niacin

Niacin reduces serum concentrations of total cholesterol, triglycerides, LDL-C, and Lp(a), while increasing HDL-C levels. These effects have been confirmed in meta-analyses including 30 clinical trials and 9,013 participants, demonstrating reductions in Lp(a) levels of up to 23%.[65,73,74]

Omega-3 Fatty Acids

Omega-3 fatty acids reduce VLDL production, increase lipoprotein lipase activity, and stimulate β-oxidation of fatty acids, which explains their triglyceride-lowering effect and potential relevance in the management of residual lipid risk when used in combination with other lipid-lowering therapies.[75] Observational and clinical studies have shown that higher circulating omega-3 fatty acid levels are associated with a lower incidence of cardiovascular disease[76] and a lower prevalence of high-risk carotid plaques.[77]

Emerging Therapeutic Strategies for Dyslipidemia

Bempedoic acid, an adenosine triphosphate-citrate lyase (ACL) inhibitor, reduces all major atherogenic lipid markers, including LDL cholesterol (LDL-C), non-HDL cholesterol, and apolipoprotein B, while also lowering high-sensitivity C-reactive protein (hsCRP), suggesting additional anti-inflammatory properties.[65] Compared with statins, bempedoic acid has been associated with a lower incidence of muscle-related adverse effects, making it an attractive option for patients with statin intolerance.[78]

Another antisense oligonucleotide, pelacarsen (APO(a)-LRx), targets hepatic LPA messenger RNA, thereby inhibiting apolipoprotein(a) synthesis and reducing lipoprotein(a) [Lp(a)] production.[79] In a phase II randomized placebo-controlled trial, pelacarsen reduced circulating Lp(a) concentrations by up to 80%.[80] The phase III Lp(a) HORIZON trial is expected to determine whether this profound reduction in Lp(a) translates into improved cardiovascular outcome.[81]

Cholesteryl ester transfer protein (CETP) inhibitors interfere with the bidirectional exchange of cholesteryl esters and triglycerides among circulating lipoproteins, resulting in increased HDL cholesterol concentrations and reduced LDL and VLDL cholesterol levels, thereby exhibiting potentially anti-atherogenic properties.[82] Nevertheless, despite favorable effects on lipid profiles, clinical trials have not consistently demonstrated meaningful cardiovascular benefit or convincing effects on the progression of subclinical atherosclerosis.[83] Nanotechnology is emerging as a promising field in preventive cardiology. Nanoparticle-based delivery systems are increasingly being investigated for the targeted administration of statins and RNA-based therapeutics, improving drug bioavailability, enhancing solubility, enabling controlled drug release, and potentially reducing systemic toxicity and adverse effects.[84]

Recently approved lipid-modifying therapies, including APOC3 inhibitors and ANGPTL3 inhibitors, have expanded treatment options for patients with severe or treatment-resistant dyslipidemia and persistent residual atherosclerotic cardiovascular risk.[85,86]

Growing attention has also been directed toward triglyceride-rich lipoprotein (TGRL)-targeted therapies, particularly omega-3 fatty acids, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). These agents effectively reduce triglyceride concentrations, while cardiovascular outcome benefits have been demonstrated primarily with highly purified EPA formulations in appropriately selected high-risk patients.[87]

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), widely used in the treatment of type 2 diabetes and obesity, reduce body weight, body mass index (BMI), and glycated hemoglobin (HbA1c), while also producing modest improvements in LDL cholesterol and triglyceride concentrations.[88] A meta-analysis and meta-regression of randomized placebo-controlled trials confirmed their favorable effects on total cholesterol and LDL-C levels.[89] Beyond lipid modification, these agents provide substantial cardiovascular protection through multiple complementary mechanisms.

Muvalaplin is a novel investigational oral agent that selectively inhibits lipoprotein(a) formation. Results from a phase II randomized clinical trial demonstrated a marked reduction in circulating Lp(a) concentrations after 12 weeks of treatment without significant safety concerns.[90]

Despite well-established guideline recommendations for lipid-lowering therapy, initiation and intensification of treatment remain suboptimal in everyday clinical practice, particularly among asymptomatic individuals. This therapeutic inertia is likely attributable to underrecognition of subclinical atherosclerosis and excessive reliance on conventional cardiovascular risk prediction models. In this context, coronary artery calcium scoring (CACS) may play a pivotal role in overcoming therapeutic inertia by identifying patients with a moderate coronary artery calcium score (CACS 100–299 AU) who are likely to benefit from earlier and more intensive lipid-lowering therapy.

Coronary Artery Calcium Score and Therapeutic Recommendations

The 2019 European Society of Cardiology (ESC)/ European Atherosclerosis Society (EAS) Guidelines recommend initiation of high-intensity statin therapy at the maximally tolerated dose to achieve LDL-C targets according to the individual's cardiovascular risk category. If LDL-C goals are not achieved, ezetimibe should be added. Greater treatment intensity results in proportionally larger reductions in LDL-C, and in patients with higher baseline LDL-C concentrations this translates into greater absolute cardiovascular risk reduction. In very-high-risk patients undergoing secondary prevention who fail to achieve LDL-C targets despite maximally tolerated statin therapy combined with ezetimibe, addition of a PCSK9 inhibitor is recommended. Similarly, patients with familial hypercholesterolemia and very high cardiovascular risk may require combination therapy with a maximally tolerated statin and a PCSK9 inhibitor, whereas ezetimibe should be considered in those with statin intolerance.[37]

According to the American Heart Association (AHA)/ American College of Cardiology (ACC) guidelines, adults aged 40–75 years without diabetes mellitus who have LDL-C concentrations ≥70 mg/dL and an estimated 10-year ASCVD risk ≥7.5% should receive moderate- to high-intensity statin therapy. High-intensity statins are recommended when the estimated ASCVD risk is ≥20%, aiming for at least a 50% reduction in LDL-C levels. Additional cardiovascular risk-enhancing factors may further support treatment intensification. Patients at intermediate risk should generally receive moderate-intensity statin therapy, with ezetimibe considered if LDL-C targets are not achieved despite maximally tolerated statin treatment.[91]

Selection of an appropriate cardiovascular risk prediction algorithm remains fundamental to decisions regarding lipid-lowering therapy. A comparative study evaluating recommendations for statin therapy in primary prevention demonstrated considerable disagreement among different cardiovascular risk prediction models, including the Framingham Risk Score, Pooled Cohort Equations (PCE), SCORE2, and MESA. In a simulated population of 7,680 individuals, agreement between these models ranged from only 19% to 85%.[54] These findings underscore the importance of complementary imaging modalities, particularly CACS and coronary computed tomography angiography, for refining cardiovascular risk assessment.

Coronary artery calcium scoring has become an established imaging biomarker of subclinical coronary atherosclerosis and an important tool for cardiovascular risk assessment in primary prevention. Individuals with CACS = 0 AU generally have an excellent prognosis and may often be managed conservatively in the absence of additional major risk factors. Conversely, increasing coronary calcium burden is associated with progressively higher cardiovascular risk, supporting more intensive lipid-lowering therapy and stricter lipid target achievement.[92]

The AHA/ACC Primary Prevention Guidelines emphasize the role of CACS in personalizing statin therapy. In individuals with CACS = 0 AU, statin therapy may be deferred if no major cardiovascular risk-enhancing factors are present. A CACS of 1–99 AU favors statin therapy, particularly in individuals older than 55 years, whereas CACS 100–299 AU strongly supports initiation and intensification of statin treatment. Analysis of more than 16,000 participants demonstrated that CACS-guided decision making may avoid unnecessary statin therapy in 60–80% of middle-aged adults while simultaneously identifying older individuals who are most likely to benefit from treatment.[93]

Increasing evidence suggests that patients with a moderate coronary artery calcium score (CACS 100–299 AU) should not simply be regarded as having intermediate cardiovascular risk. In many of these individuals, the actual cardiovascular risk more closely resembles that observed in high-risk populations, supporting consideration of earlier and more intensive preventive treatment strategies.

Conclusions

Patients with subclinical coronary atherosclerosis and a moderate coronary artery calcium score (CACS 100–299 AU) represent a heterogeneous population in whom conventional cardiovascular risk prediction models frequently underestimate the true burden of disease. Coronary artery calcium scoring provides powerful incremental prognostic information beyond traditional risk algorithms and facilitates earlier identification of individuals who are likely to derive substantial benefit from lipid-lowering therapy.

Current evidence demonstrates that intensive LDL-C reduction with high-intensity statins, supplemented when necessary by ezetimibe or PCSK9 inhibitors, slows the progression of atherosclerotic plaque development and reduces future cardiovascular events. At the same time, the therapeutic landscape continues to evolve with the introduction of novel agents, including bempedoic acid, antisense oligonucleotides, small interfering RNA (siRNA)-based therapies, and other targeted lipid-lowering strategies, allowing increasingly individualized cardiovascular prevention.

Taken together, the available evidence supports considering patients with a moderate coronary artery calcium score (CACS 100–299 AU) as an important subgroup in whom earlier and more intensive lipid-lowering therapy may be justified despite apparently intermediate cardiovascular risk according to conventional prediction models.

Limitations

This narrative review has several limitations. The literature search was restricted to the PubMed/MEDLINE database and English-language publications, which may have resulted in the omission of relevant studies indexed elsewhere or published in other languages. In addition, as a narrative review, the evidence was synthesized descriptively rather than through a formal systematic review methodology, and no standardized assessment of study quality or risk of bias was performed. Finally, the available evidence specifically addressing lipid-lowering strategies in patients with moderate coronary artery calcium scores (CACS 100–299 AU) remains limited,

highlighting the need for further prospective studies to better define optimal therapeutic strategies.

Conflict of Interest

The authors declare that they have no competing interests.

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